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The Synthesis of Some Aromatic Hydrocarbons

A DISSERTATION

SUBMITTED TO THE SCHOOL OF GRADUATE STUDIES

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF MASTER OF SCIENCE

FACULTY OF ARTS AND SCIENCES

by

L. R. Melby, B. Sc.

EDMONTON, ALBERTA

April, 1950

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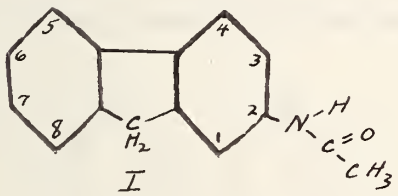
PART I

THE SYNTHESIS OF SOME SUBSTITUTED BIPHENYLS

INTRODUCTION

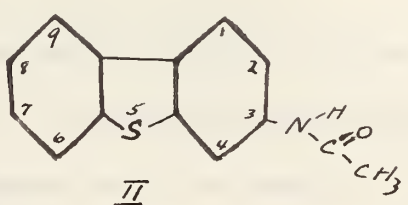
It has been demonstrated by Wilson, De Eds and Cox (1), and other workers, that 2-acetylaminofluorene (I)



I

is a powerful carcinogen capable of producing malignant tumors in mammary gland, ear duct and liver tissue in rats. This work has stimulated the investigation of certain analogues of I with a view to determining their carcinogenic effects, if any. Miller, Miller, Sandin and Brown (2) have carried out work of this nature with analogues of I in which the methylene linkage in I has been substituted by a thio-ether linkage, a sulfoxide linkage and an ether linkage.

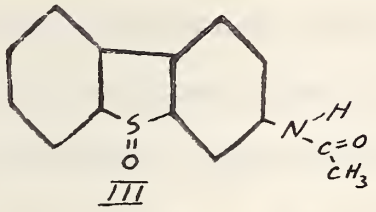
It was found (2) that 3-acetylaminodibenzothiophene (II),



II

which contains the thio-ether linkage, retains the carcinogenicity of I toward mammary gland and ear duct tissue but has no effect on the liver of rats.

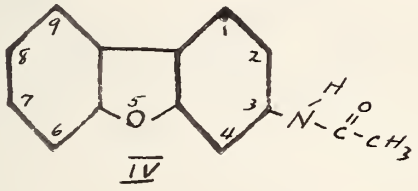
The introduction of the sulfoxide linkage gave 3-acetylamino-dibenzothiophene-5-oxide (III)



III

which proved to be only feebly active toward mammary gland and ear duct tissue.

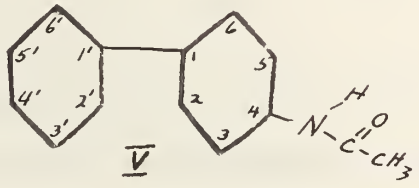
On the other hand, 3-acetylaminodibenzofuran (IV)



IV

showed marked activity toward mammary gland tissue but reduced activity toward the ear duct and was completely inactive toward liver tissue.

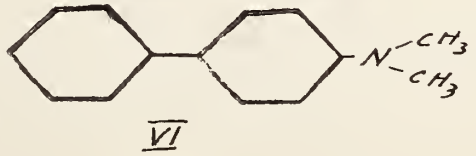
It is evident that compounds I, II, III and IV consist of a 4-acetylaminobiphenyl nucleus (V),



V

the 2 and 2′ positions of which have been bridged by a particular group or atom. The similarity in structure between V and the other carcinogens referred to above, suggested that V be tested for activity. It was found (3) that V has pronounced tumour producing ability.

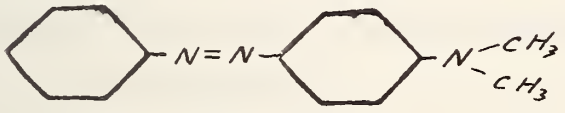
Moreover, 4-dimethylaminobiphenyl (VI)



VI

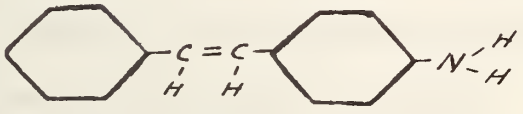
was found (2) to be capable of producing tumors at numerous sites in the rat.

In addition to having structures analogous to the carcinogenic derivatives of fluorene and its analogues, these biphenyl derivatives have structures similar to the carcinogenic aminoazo dyes except that they lack the -N=N- linkage present in the latter. In fact VI was originally tested (2) for activity as an analogue of the hepatic carcinogen 4-dimethylamino-azobenzene (VII).



VII

Further, relative to present considerations, the very interesting work of Haddow and co-workers (4) has revealed that 4-aminostilbene (VIII)



VIII

and certain of its derivatives are active carcinogens. The structural analogy between the biphenyl and stilbene derivatives at once becomes apparent.

In an attempt to correlate these data and to justify the experimental work carried out in this part of this thesis, a consideration of the structure of biphenyl (IX)

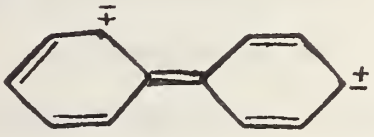
IX

must first be carried out.

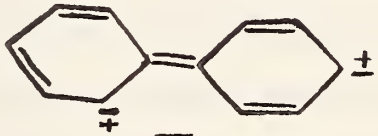
Several resonating electronic structures contribute to the overall structure of biphenyl in addition to the Kekulé resonance within the benzene rings. One of the important contributors is believed to be the one in which a separation of charge occurs giving rise to the para-quinonoid form (IXa).

IX a

The bond between the two rings is known to have some double bond character. In addition, forms IXb and IXc



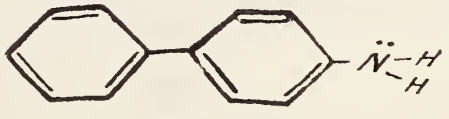
IX b



IX c

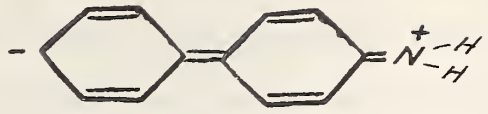
must not be discounted, however, for explanation purposes, let it suffice to refer only to the para-quinonoid forms henceforth.

In these resonating structures the quinoidation and charge separation are accompanied by a coplanar arrangement of the two benzene rings. Indeed the presence of the double bond between the two rings forces the latter into the same plane. If now, an electron doning group, such as the amino group, is introduced into the para or 4 position of one of the benzene rings, the tendency for the quinonoid structures to exist would be enhanced since electrons are more readily donated by the amino nitrogen than by a benzenoid carbon. Consequently, in the overall structure of 4-aminobiphenyl (X)



X

the para-quinonoid form Xa

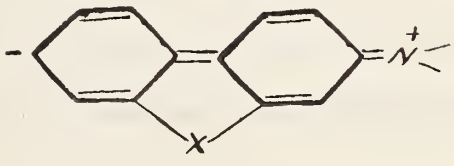


Xa

would be a major contributor. Indeed, studies on the absorption spectra of biphenyl and of 4-aminobiphenyl (5) have shown that the large extinction shown by biphenyl, due to what is now known to be the quinonoid contributor, is shifted to a longer wave length (shorter frequency) when the 4-amino group is introduced into the biphenyl nucleus. This indicates that less energy is required to bring about coplanarity in the 4-aminobiphenyl as compared to the unsubstituted biphenyl.

In considering the carcinogenicity of 4-dimethylaminobiphenyl or 4-acetylaminobiphenyl it is not unreasonable to assume that the compounds become bound, in some fashion, to the tissue in which carcinogenisis takes place. Indeed a structure such as Xa should be very well adapted for such binding, not only because of its flat shape, giving effectively a large binding surface, but also because of the proton and electron seating effect of the areas of high and low electron density in the molecule. It is feasible that these effects could bring about a union between the carcinogen and the tissue protein.

In 2-acetylaminofluorene, and its carcinogenic analogues, the molecule is held in a uniplanar state by the unit which bridges the two benzene rings. Structures such as XI



XI

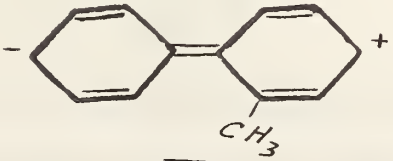
may readily exist in a molecule of this nature.

In view of all these observations, it seems feasible that if the structure of the carcinogenic 4-acetylaminobiphenyl could be modified in some manner so as to minimize or prevent contributions to its structure by coplanar quinonoid forms such as Xa, then its carcinogenicity might be reduced or completely lost.

Studies by Friedel, Orchin and Reggel (6), on the ultra-violet absorption spectra of biphenyl, show that a large maximum in the extinction curve exists at a wave length of 2500 Angstrom units. This maximum is attributed to the para-quinonoid resonance form since it is the most important for light absorption. If now one ortho hydrogen of the biphenyl molecule is substituted by a methyl group the 2-methylbiphenyl molecule (XII)

XII

is formed. Its extinction curve shows that the maximum, due to the optically important para-quinonoid structure, has been shifted to a shorter wave length and reduced in intensity. Evidently the extent of contribution by a form such as XIIa

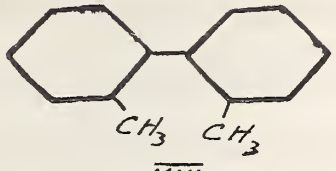


XIIa

to the overall structure of XII is reduced, since the steric hindrance of the methyl group makes it difficult for the two rings to become coplanar.

Similar studies by Rodebush and O'Shaughnessy (7) have shown

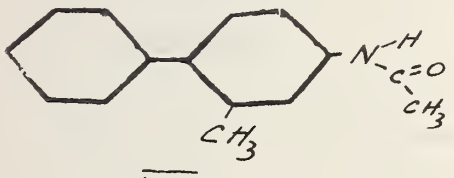
that coplanarity is largely prevented in 2,2′-dimethylbiphenyl (XIII).



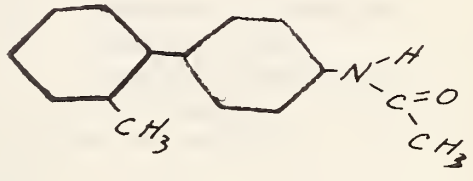
XIII

The work of Sherwood and Calvin (8) on 2,2′-dimethyl-4-amino-4′-nitrobiphenyl might also be noted in this regard.

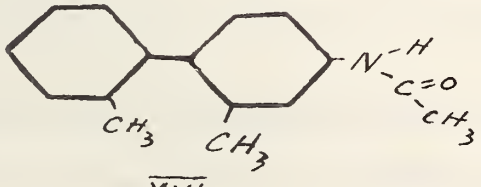
The purpose of the work in this part of this thesis was then, to carry out the preparation of three compounds related to the carcinogenic 4-acetylaminobiphenyl. Those compounds are 2-methyl-4-acetylaminobiphenyl (XIV), 4-acetylamino-2′-methylbiphenyl (XV) and 2,2′-dimethyl-4-acetylamino-biphenyl (XVI)



XIV



XV



XVI

These compounds contain the 4-acetylaminobiphenyl nucleus but also have methyl substituents in positions which would inhibit the resonance responsible for the formation of uniplanar forms. On testing them for carcinogenicity, it would be hoped that they would show either complete lack of activity, or at least reduced activity compared to 4-acetylamino-biphenyl. Such a result would give evidence to the theory that coplanarity

at least, and perhaps a high degree of charge separation resonance, are fundamental prerequisites in bestowing upon 4-acetylaminobiphenyl, and its analogues, the ability to produce cancerous tumors.

At this writing, a communication from Drs. J. A. Miller and E. C. Miller of the McArdle Memorial Laboratory, University of Wisconsin, informs us of the results of the animal work with compounds XIV and XV. In October of 1949, these workers began feeding three groups of rats standard diets. The diets of one group (the control group) contained 2-acetylaminofluorene (I), of another XIV and of the third XV. The following table summarizes the results after treatment of the rats for five months.

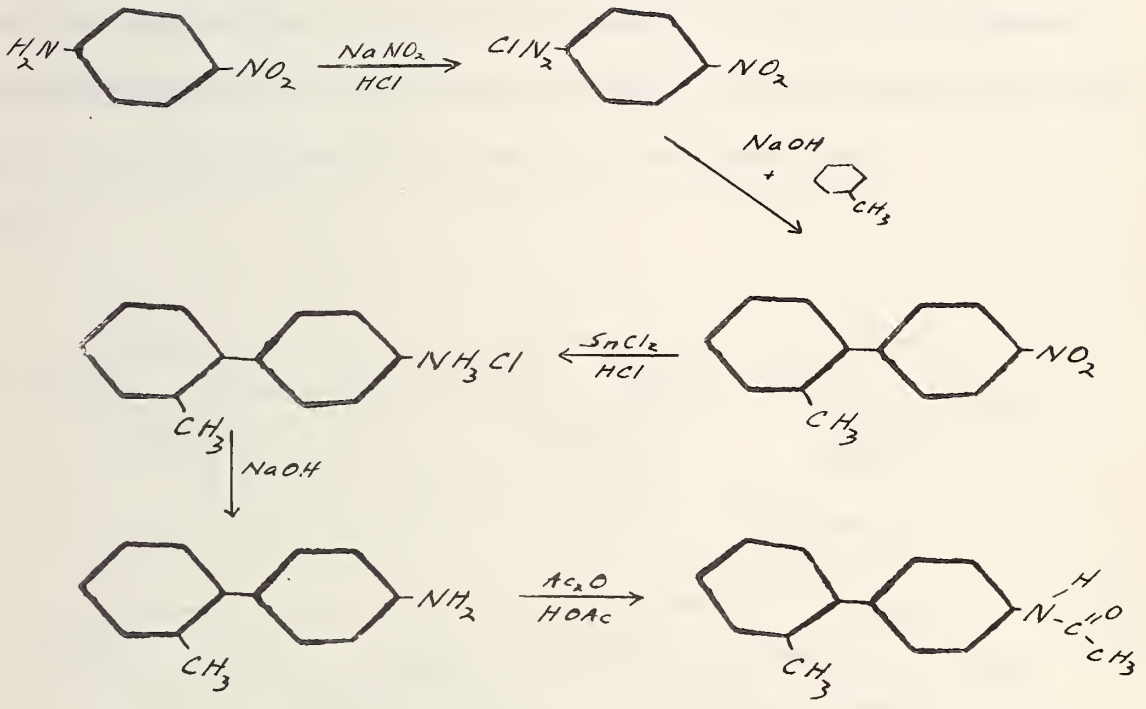
Compound	No. of rats sacrificed	No. bearing tumors	Location of tumors
I (control)	9	6	Mammary in females. Ear and liver tumors starting in males.
XIV	9	0	
XV	9	0	

A control series with 4-acetylaminobiphenyl (V) was not run concurrently with the above series, since in a typical experiment with that compound, Miller and Miller have found that after treatment for five months, four out of seven female rats bore mammary tumors, indicating that V is as active as I in mammary tumor production.

These results seem to bear out the theory suggested in this thesis.

DISCUSSION

The following flow sheet illustrates the method by which the known 4-acetylamino-2′-methylbiphenyl was prepared. The method was essentially that used by France, Heilbron and Hey (9) in the preparation of that compound.



The initial preparation of the 4-nitro-2′-methylbiphenyl is an application of the procedure developed by Gomberg for the preparation of biaryls.

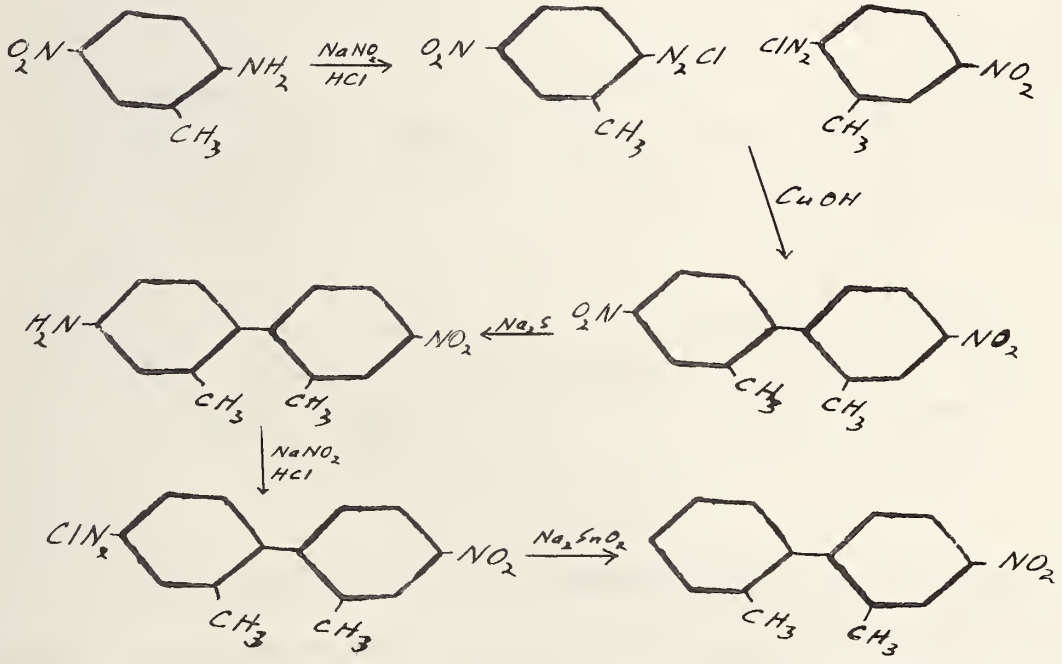
The 4-amino-2′-methylbiphenyl, though previously isolated, had not been characterized, consequently, in the present work, this was done. The very insoluble hydrochloride of this amine was isolated and also characterized.

The new compound, 2-methyl-4-acetylaminobiphenyl, was prepared in essentially the same way. The known 2-methyl-4-nitrobiphenyl (10) was

prepared by the Gomberg reaction with diazotized 2-amino-5-nitrotoluene and benzene. The nitro compound was then converted to the amine, aminehydrochloride and acetylamine, all of which were characterized.

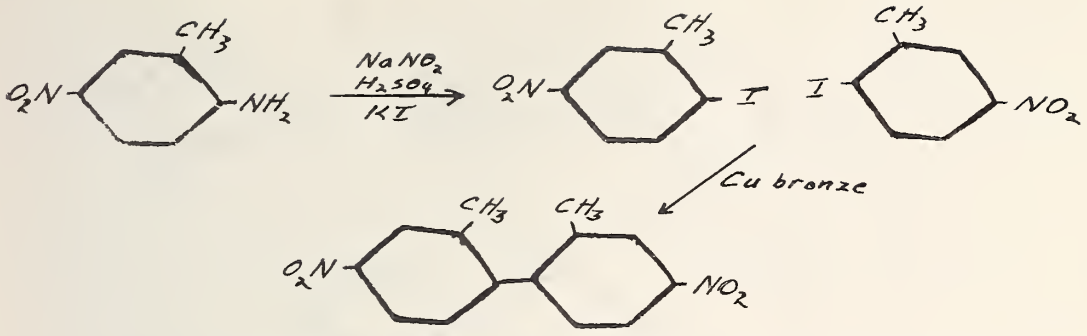
The third compound in this series, the 2,2′-dimethyl-4-acetylaminobiphenyl, proved to be most difficult to synthesize. Obviously if the corresponding nitro compound could be obtained the acetylamine could be readily prepared from it, so the following discussion will consider attempted preparations of that nitro compound. In all, eight routes suggested themselves and all proved fruitless. A ninth route now in the process of investigation has, as yet, not been completed.

ROUTE I



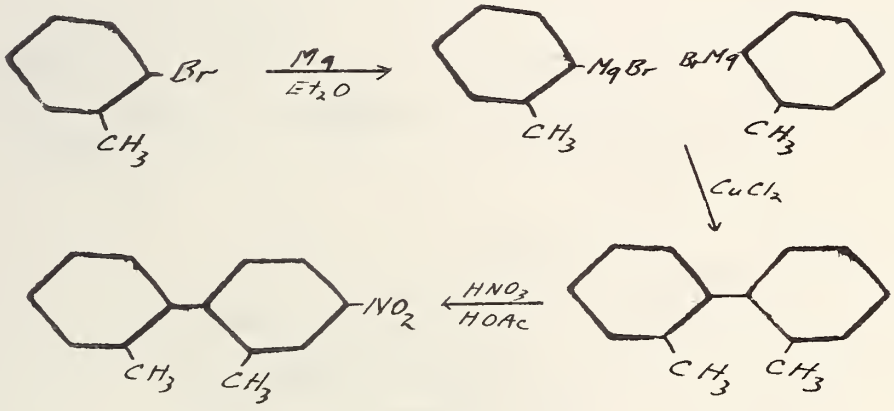
Though Sherwood and Calvin (8) and Le Fevre and Vine (11) have carried out the preparation of the dinitrodimethylbiphenyl, as shown, yet several attempts by the present author failed to duplicate their results so this route was abandoned.

ROUTE II



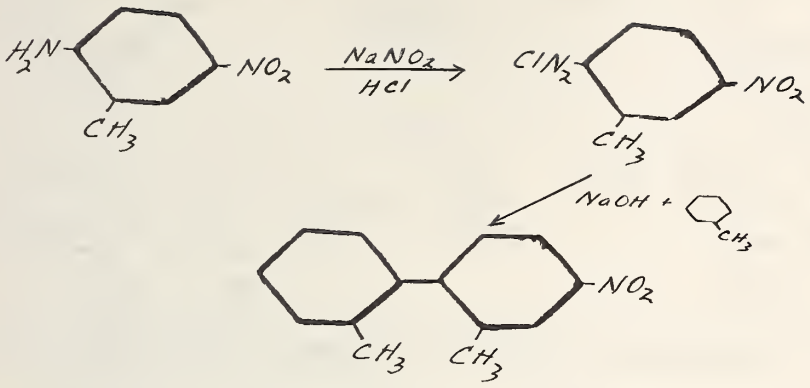
The Ullmann reaction with copper powder and the iodo compound shown failed to produce anything but a small amount of m-nitrotoluene. A similar Ullmann on the corresponding bromo compound failed also.

ROUTE III



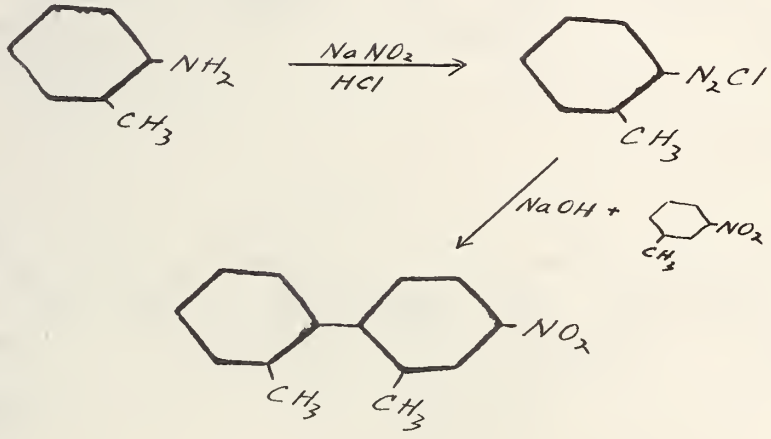
The nitration of the 2,2′-dimethylbiphenyl was attempted according to a procedure developed for the nitration of 4,4′-dimethylbiphenyl (12) but gave only unchanged starting material.

ROUTE IV



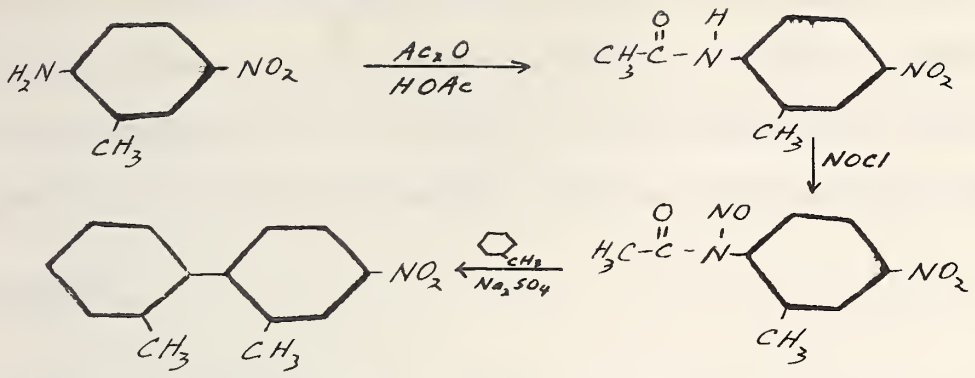
The attempted Gomberg reaction with diazotized 2-amino-5-nitrotoluene and toluene succeeded only in reducing the diazonium salt to m-nitrotoluene.

ROUTE V



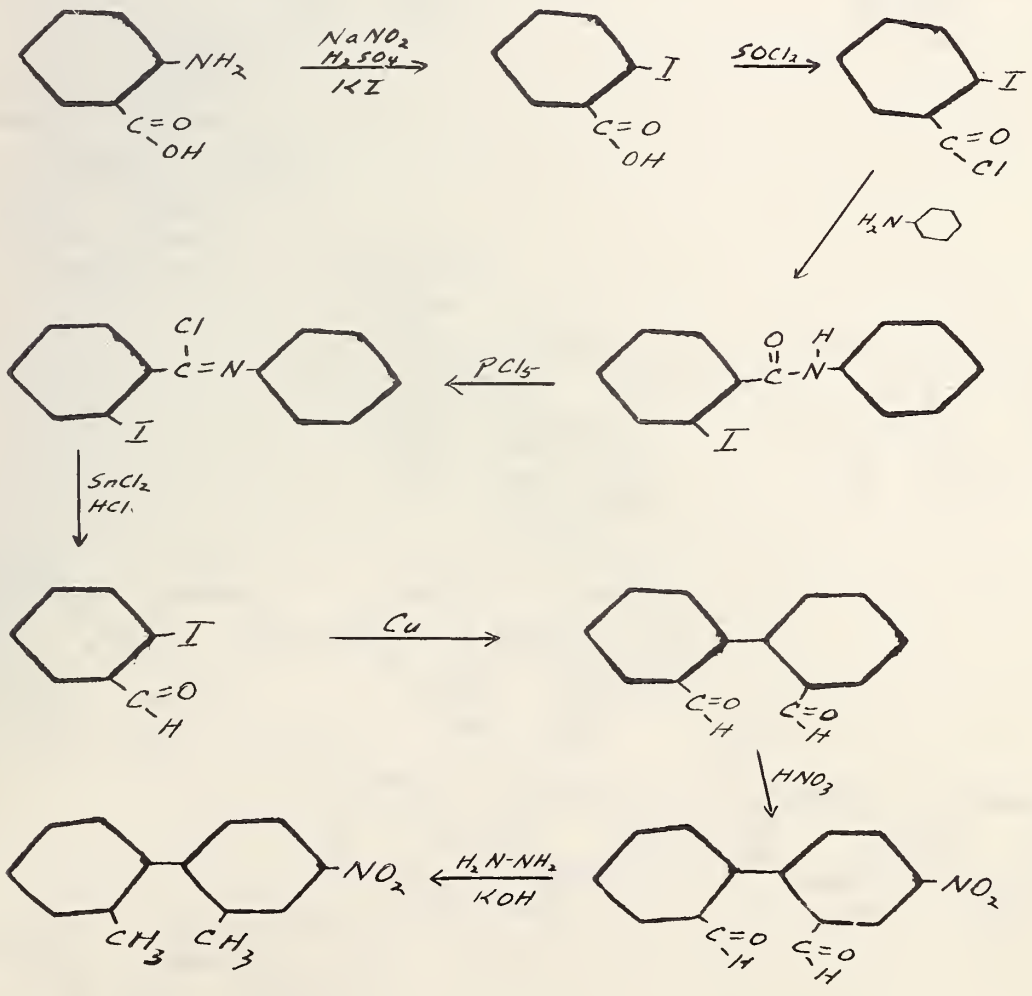
The above Gomberg reaction produced a tar from which no identifiable products could be isolated.

ROUTE VI



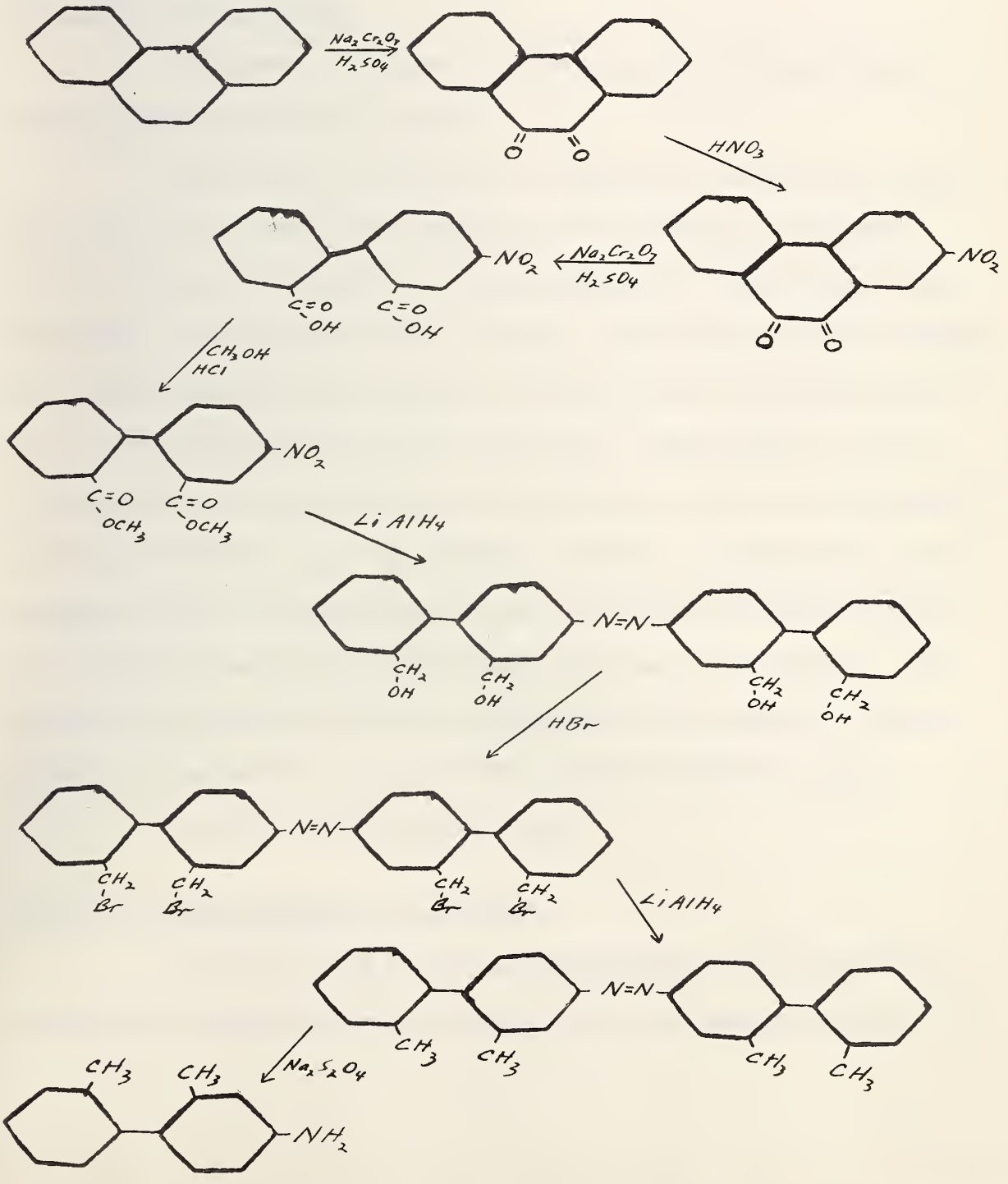
The reaction between the nitroso derivative of 2-acetylamino-4-nitrotoluene and toluene succeeded only in releasing the free 2-acetylamino-4-nitrotoluene.

ROUTE VII



Having prepared the 2,2′-dialdehydrobiphenyl (13) it was thought wise that a Huang-Minlon-Wolf-Kishner reduction be attempted on it to determine whether the aldehyde groups could be converted to methyl groups. Since this reduction failed utterly, it was assumed that it would not succeed on the nitrated dialdehyde, therefore this route was abandoned.

ROUTE VIII



The dimethyl ester of 4-nitrodiphenic acid was readily prepared, but reduction of it with lithium aluminum hydride gave an orange, crystalline, high melting solid which could not be purified for analysis.

EXPERIMENTAL PART

All melting points and boiling points are uncorrected.

4-Nitro-2′-methylbiphenyl

The procedure of France, Heilbron and Hey (9) was followed in the preparation of this compound.

Diazotized p-nitroaniline in toluene was treated with sodium hydroxide solution and after completion of the reaction the toluene layer was separated from the acidified mixture. The tarry residue was thoroughly extracted with boiling toluene. The combined toluene extracts were concentrated at reduced pressure and the viscous oil remaining was distilled under high vacuum using a salt bath. The forerun boiling up to 180° at 5 mm. was discarded and the yield of 4-nitro-2′-methylbiphenyl boiling at 180°-185° and 5 mm. pressure was 30 g. To remove any of the isomeric 4-nitro-4′-methylbiphenyl, this product was redistilled and 26 g. of the fraction boiling at 187°-188° and 3 mm. was collected. This product was crystallized twice from 95% ethanol and separated as small, slightly yellow needles, m.p. 97°-100°, (reported 102°-103°) (9).

The final yield was 24 g. (12%).

4-Amino-2′-methylbiphenyl Hydrochloride

Ten grams of the 4-nitro-2′-methylbiphenyl was refluxed for one-half hour with 95% ethanol containing 70 g. of stannous chloride and

70 cc. of concentrated hydrochloric acid. The mixture was poured, with stirring, into 500 cc. of water. On cooling, the solution precipitated beautiful white platelettes of the amine hydrochloride in almost quantitative yield.

This hydrochloride was crystallized twice from water and melted at 285° with decomposition.

Anal. Calcd. for $C_{13}H_{14}NCl$: Cl, 16.1. Found: Cl, 15.9; 16.1

4-Amino-2′-methylbiphenyl

This amine was released by heating the hydrochloride with excess sodium hydroxide solution.

The amine was extracted with ether, the extract dried over sodium sulfate and after removal of the ether the amine was distilled at reduced pressure. The amine obtained in 75% yield was an oil boiling at 190° and 23 mm.

Anal. Calcd. for $C_{13}H_{13}N$: C, 85.2; H, 7.2. Found: C, 85.3; H, 7.1.

4-Acetylamino-2′-methylbiphenyl

Ten grams of the amine was refluxed for fifteen minutes with 10 cc. of acetic anhydride in 30 cc. of glacial acetic acid. The hot mixture was poured into a large excess of water and thoroughly cooled. The solid product was filtered, crystallized three times from dilute ethanol and so, finally obtained in 80% yield as fine white needles, m.p. 143°-144°, (reported 146°-147°) (9).

2-Methyl-4-nitrobiphenyl

This compound was prepared through the Gomberg reaction with diazotized 2-amino-5-nitrotoluene and benzene in the same way as the

above isomeric nitro compound.

This nitro compound distilled at 170° and 4 mm. pressure and was obtained in 15% yield. On crystallization from 95% ethanol, it melted at 55°-56°, (reported 56°-57°) (10).

2-Methyl-4-aminobiphenyl Hydrochloride

2-Methyl-4-nitrobiphenyl was reduced in the same manner as the isomeric nitro compound.

The amine hydrochloride crystallized from water as white platelettes, m.p. 270° with decomposition.

Anal. Calcd. for $C_{13}H_{14}NCl$: Cl, 16.1. Found: Cl, 15.5; 15.6.

2-Methyl-4-aminobiphenyl

This amine was obtained in 80% yield by releasing it from the hydrochloride in the usual way. It was an oil boiling at 178° and 12 mm.

Anal. Calcd. for $C_{13}H_{13}N$: C, 85.2; H, 7.2. Found: C, 85.7; H, 7.2.

2-Methyl-4-acetylaminobiphenyl

Acetylation of the amine with acetic anhydride and acetic acid gave an 80% yield of this compound. It crystallized from dilute ethanol as white platelettes, m.p. 125°.

Anal. Calcd. for $C_{15}H_{15}ON$: C, 80.0; H, 6.7. Found: C, 80.6; H, 6.7.

BIBLIOGRAPHY

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(4) Haddow et al, Phil. Trans. Roy. Soc. London, Series A, 241, 147 (1948).

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(6) Friedel, Orchin and Reggel, J. Am. Chem. Soc., 70, 199 (1948).

(7) Rodebush and O'Shaughnessy, ibid., 62, 2906 (1940).

(8) Sherwood and Calvin, ibid., 64, 1350 (1942).

(9) France, Heilbron and Hey, J. Chem. Soc., 1287 (1939).

(10) Bamberger, Ber., 28, 403 (1895).

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(12) Marler and Turner, ibid., 2392 (1932).

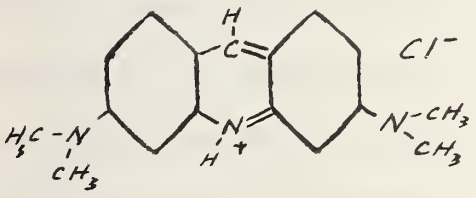
(13) Rapson and Shuttleworth, ibid., 488 (1941).

PART II

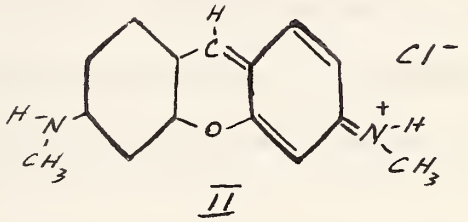
THE ADDITION OF AROMATIC GRIGNARD REAGENTS TO 4-METHOXYPHTHALIC ANHYDRIDE

INTRODUCTION

Lewis and Goland (1) have recently shown that certain dyes, such as I and II,

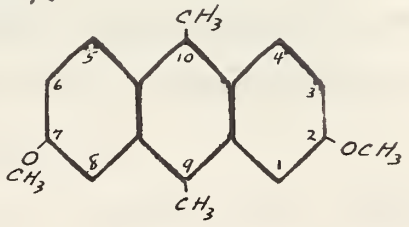


I



II

have the ability to inhibit the growth of cancerous tumors in rats. These dyes, and others structurally related to them, were fed to tumor-bearing rats with a view to staining the tumors in vivo. During the course of these staining experiments it was observed, in some instances, that remarkable retardation of tumor growth occurred. Many of the dyes which have this inhibiting ability are isosteric and so, originally, the object of this part of this thesis was to prepare 2,7-dimethoxy-9,10-dimethylanthracene (III).



III

This hydrocarbon was to be tested for tumor inhibiting ability since it is evident that, although it is not a dye, it bears at least a superficial

structural resemblance to I and II.

Compound III was indeed synthesized but during the course of its preparation certain very interesting theoretical effects were observed and so its characterization and preparation in quantity were temporarily abandoned in favor of investigating these effects.

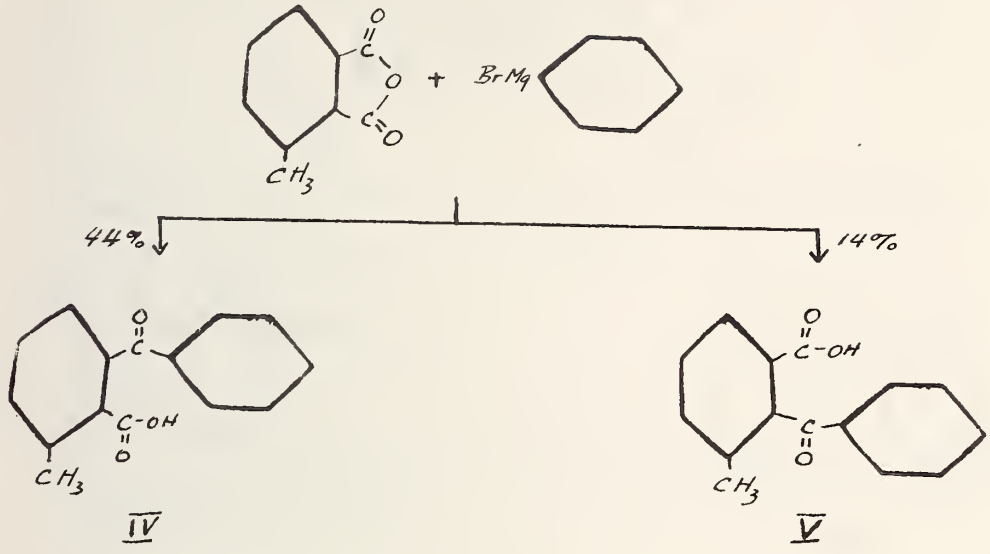
Meso-alkyl anthracenes may be prepared from the corresponding anthraquinones using the procedure developed by Sandin and Fieser (2a). (See also Sandin, Kitchen and Fieser (2b)). This procedure involves the addition of the alkyl Grignard reagent to the carbonyls of the anthraquinone, followed by treatment of the resulting adduct with hydriodic acid and reduction with stannous chloride and hydrochloric acid in dioxane.

Substituted anthraquinones may be prepared by the cyclodehydration of substituted ortho-aroylbenzoic acids. The latter may best be obtained either by the Friedel Crafts condensation of an aromatic hydrocarbon with a substituted phthalic anhydride or by the reaction of an aromatic Grignard reagent with the phthalic anhydride.

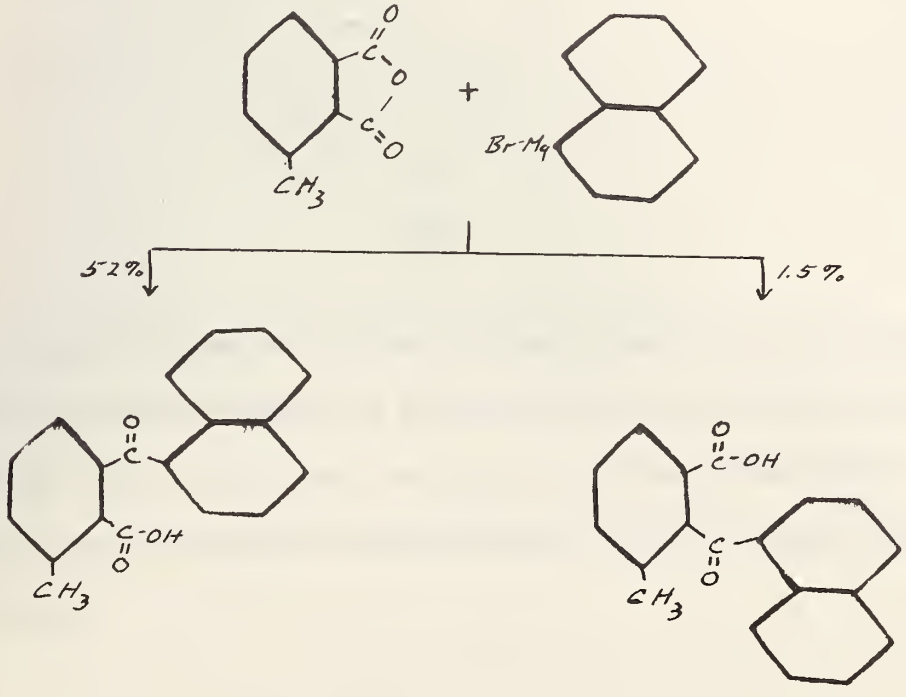
The problem of synthesizing III thus resolved itself into the problem of preparing the properly substituted ortho-benzoylbenzoic acid which could then be cyclized to the anthraquinone, followed by alkylation and reduction to the substituted anthracene. The route chosen for the preparation of the keto acid was through the aforementioned Grignard reaction.

It is to be pointed out that normally when an aromatic Grignard reagent reacts with an unsymmetrically substituted phthalic anhydride, a mixture of two isomeric ortho-aroylbenzoic acids is obtained. Thus Newman and McLeary (3a) have obtained

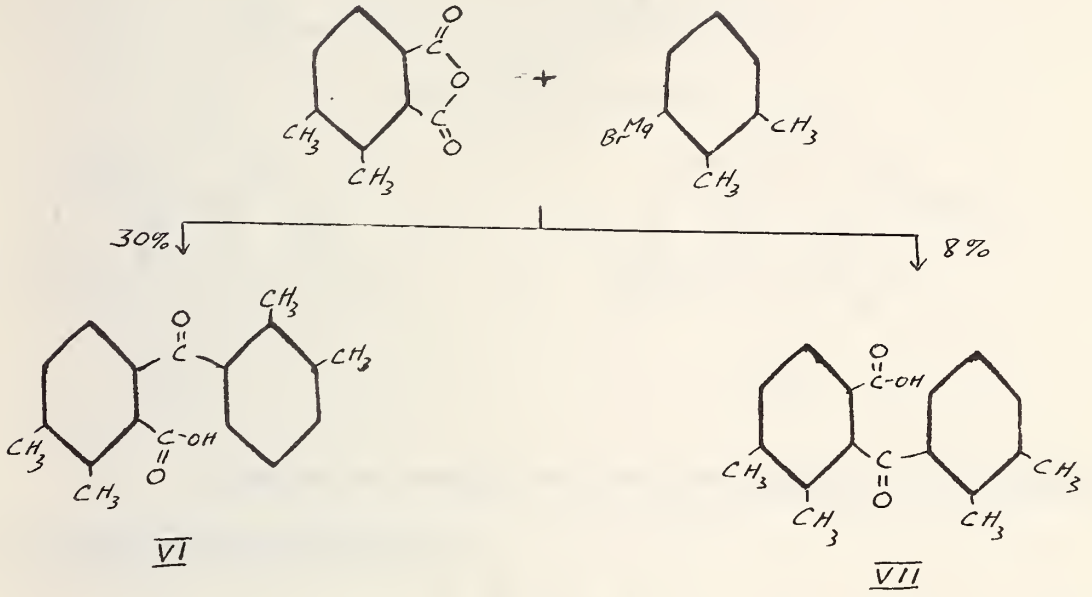
2-benzoyl-6-methylbenzoic acid (IV) and 2-benzoyl-3-methylbenzoic acid (V) by treating 3-methylphthalic anhydride with phenylmagnesium bromide according to the equation



Similarly Newman (4) prepared two isomeric keto acids according to the following:

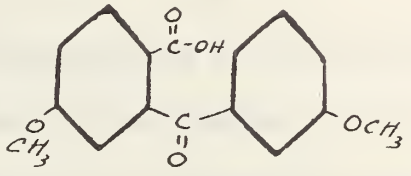


Nichol and Sandin (5) obtained similar results with the Grignard reagent of 3-bromo-o-xylene and 3,4-dimethylphthalic anhydride.



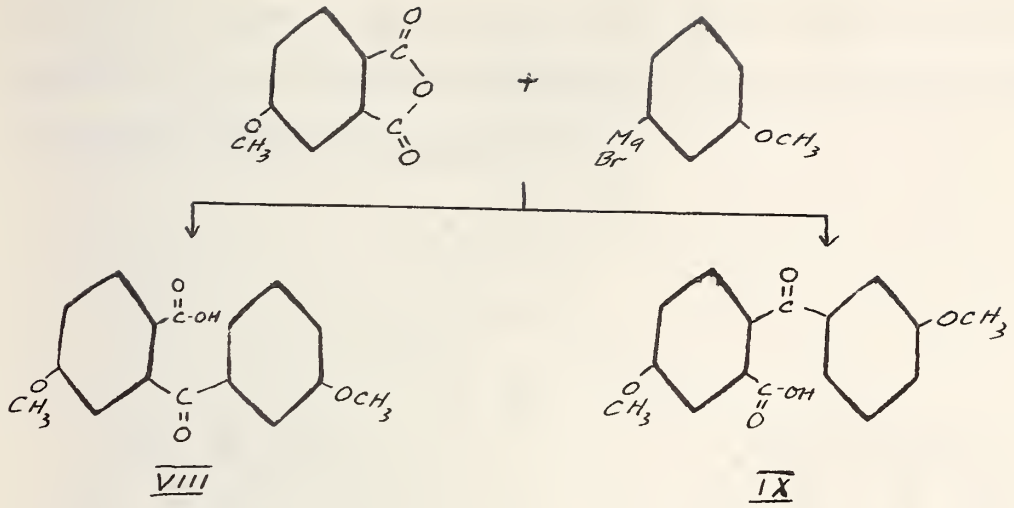
VI VII

Now the present problem required the preparation of 2-(3′-methoxybenzoyl)-4-methoxybenzoic acid (VIII).



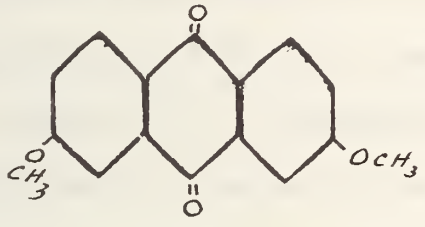
VIII

The reaction involved in this synthesis would be through the addition of the Grignard reagent of m-bromoanisole to 4-methoxyphthalic anhydride and if this reaction were to proceed as those cited above, the isomeric 2-(3′-methoxybenzoyl)-5-methoxybenzoic acid (IX) would also form as follows:



VIII IX

It might be thought that the preparation of the required 2,7-dimethoxyanthraquinone(X)

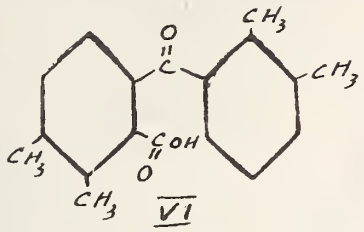


X

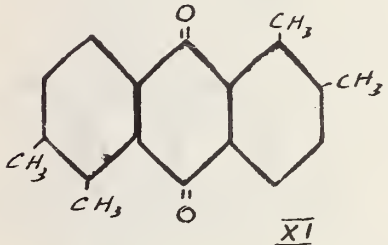
could readily be accomplished by the cyclodehydration of keto acid VIII. Generally, however, the cyclization of a pure ortho-benzoylbenzoic acid, which is unsymmetrically substituted in both benzene rings, gives not a single anthraquinone but rather a mixture of isomeric quinones. Therefore if the cyclizations of VIII and IX followed the usual course, the preparation of X by such a procedure would not be simplified by the preliminary separation of VIII from the mixture of keto acids obtained in the Grignard reaction. As will be realized IX would yield a mixture of the same quinones as VIII.

To bear this out, reference to the work of Nichol and Sandin

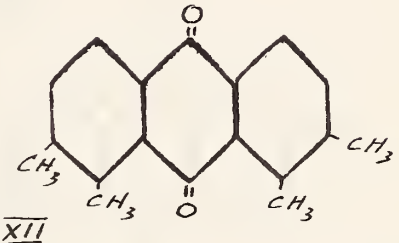
(5) is in order. These workers isolated pure keto acid VI and cyclized it with hot concentrated sulfuric acid. They obtained not only the expected 1,2,5,6-tetramethylanthraquinone (XI) but also the isomeric 1,2,7,8-tetramethylanthraquinone (XII)



VI

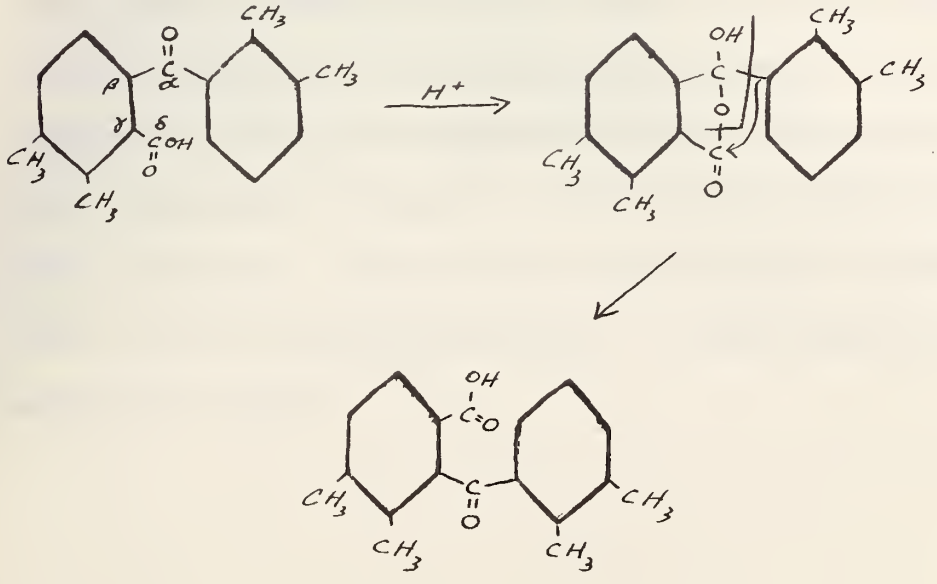


XI

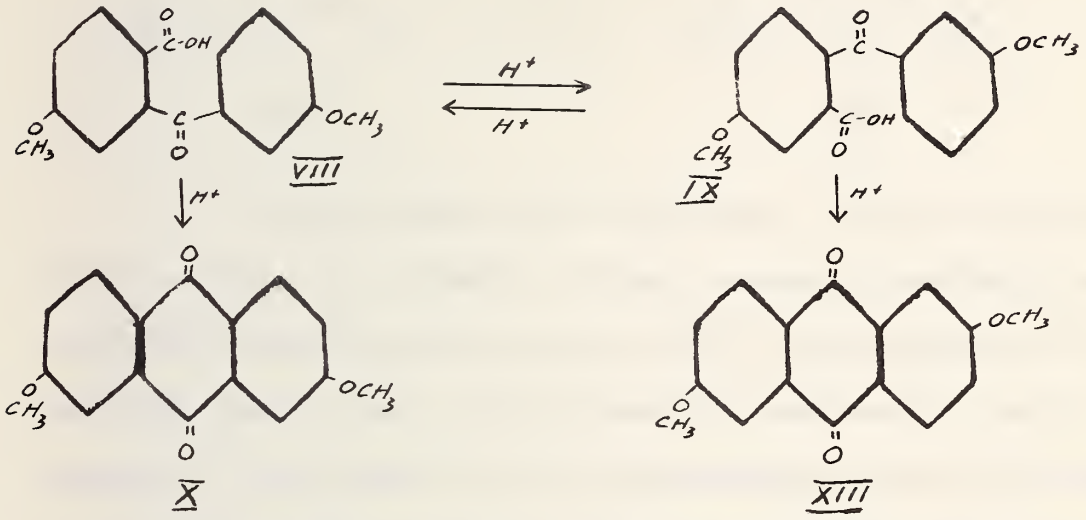


XII

This evidently involves a rearrangement of the type encountered by Hayashi (6) and elucidated by Cook (7). Apparently some of VI rearranges to the isomeric 2-(2′,3′-dimethylbenzoyl)-3,4-dimethylbenzoic acid (VII) with subsequent cyclization of the latter to XII. According to Cook's suggestion (7) this rearrangement would occur through an intermediate change of the keto acid to an hydroxylactone, followed by an α - δ migration of a substituted phenyl group as follows:

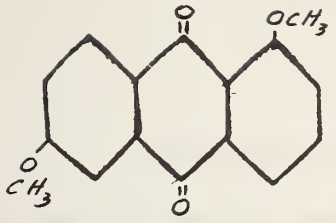


On the basis of these observations then, if, for example, pure 2-(3′-methoxybenzoyl)-4-methoxybenzoic acid (VIII) were cyclized and exhibited a similar rearrangement, the expectation would be to obtain two isomeric dimethoxyanthraquinones.

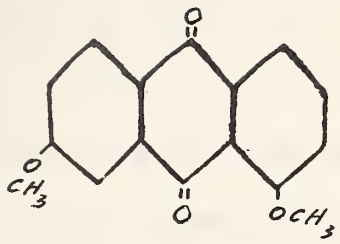


Presumably IX would produce the same two quinones through rearrangement to the isomeric VIII. Therefore, from a purely preparative standpoint, the isolation of the required 2,7-dimethoxyanthraquinone X could be most easily effected by cyclizing the keto acid mixture followed by separation of the resulting quinones.

On further consideration it becomes evident that X and XIII result from cyclization of the keto acids at positions para to the methoxy substituents in the methoxybenzoyl groups. It is feasible that cyclization could occur at positions ortho to these substituents. This would complicate the separation of the isomeric dimethoxyanthraquinones since, obviously, a mixture of four and not merely two products would result from the cyclization reaction. The additional two quinones formed would be XIV and XV.



XIV



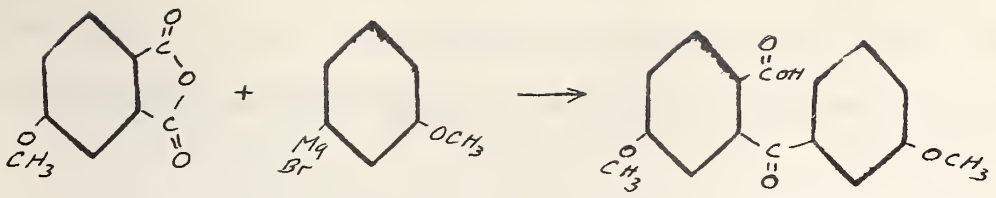
XV

To sum up these observations then, it may be said that if the addition of an aromatic Grignard reagent to 4-methoxyphthalic anhydride followed the usual course, and if the cyclization of the resulting isomeric keto acids followed the usual course, then the isolation of the desired 2,7-dimethoxyanthraquinone would ultimately resolve in the rather tedious procedure of separating it from a mixture of four isomeric dimethoxyanthraquinones.

Experimentally the present work has shown that due to certain apparently unique effects this problem is greatly simplified and is of considerable interest from a theoretical standpoint.

EXPERIMENTAL RESULTS

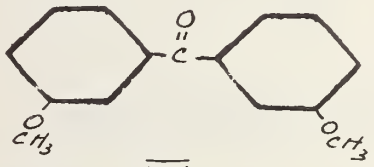
As pointed out earlier, the problem was attacked initially by the attempt to prepare 2-(3′-methoxybenzoyl)-4-methoxybenzoic acid (VIII) which would make the desired 2,7-dimethoxyanthraquinone accessible through cyclization of that keto acid. Accordingly, the Grignard reagent of m-bromoanisole was added to 4-methoxyphthalic anhydride. This reaction did not produce the expected two keto acids but rather <u>only</u> keto acid VIII, as shown by the following equation.



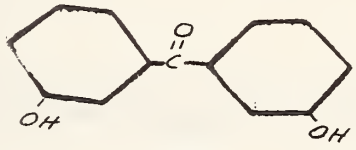
VIII

A thorough investigation of the products from the reaction and of the contents of crystallization liquors showed that no isomeric keto acids were present.

Compound VIII was characterized by analysis followed by decarboxylation to the known 3,3′-dimethoxybenzophenone (XVI) and demethylation of the latter to the known 3,3′-dihydroxybenzophenone (XVII).

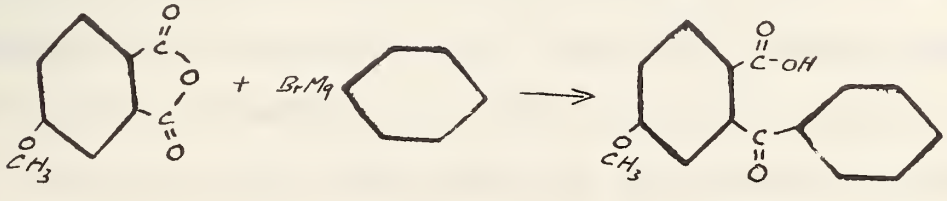


XVI



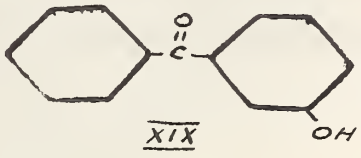
XVII

The fact that only one product is obtained in this Grignard reaction indicates that 4-methoxyphthalic anhydride behaves in a rather unique manner when compared to other unsymmetrical phthalic anhydride derivatives. That this unique behavior depends upon the properties of the anhydride was verified by results of three similar reactions, the first by addition of phenylmagnesium bromide to that anhydride.



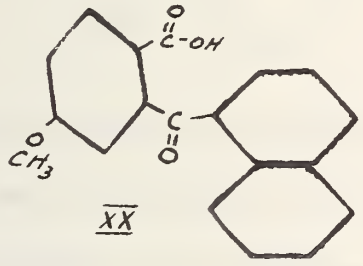
XVIII

The single product, 2-benzoyl-4-methoxybenzoic acid (XVIII), was characterized by degradation to the known 3-hydroxybenzophenone (XIX).



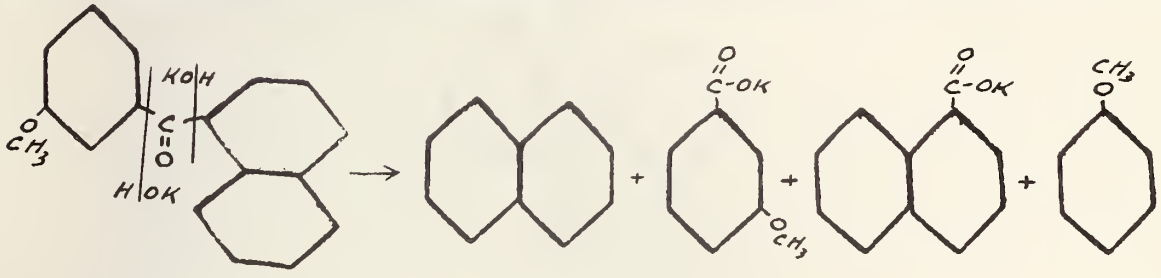
XIX

Addition of 1-naphthylmagnesium bromide to 4-methoxyphthalic anhydride gave only 2-naphthoyl-4-methoxybenzoic acid (XX).



XX

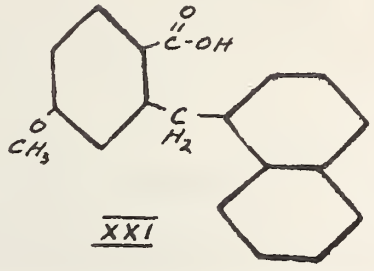
The latter was characterized by decarboxylation and cleavage of the resulting ketone by fusion with potassium hydroxide. This cleavage could produce four compounds in agreement with the following equation.



Of the four expected products, three were identified. The fourth, anisole, evidently vaporized during the fusion and so was lost. In the cleavage of unsymmetrical ketones Bachmann (8) found that a hindered group is easily separated from the carbonyl. The results of present work are in agreement with this since in this fusion relatively large amounts of naphthalene

and m-methoxybenzoic acid were obtained, but only a very small amount of 1-naphthoic acid.

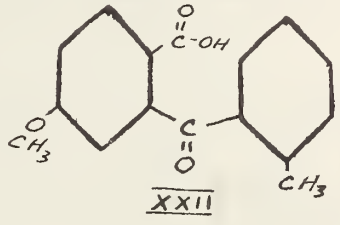
Reduction of XX with zinc dust and alkali afforded a good yield of the heretofore unknown 1-naphthyl-(2-carboxy-5-methoxyphenyl) methane (XXI).



XXI

It might be pointed out that Weizmann, Bergmann and Bergmann (9) had previously prepared XVIII and XX but these workers neglected to characterize these compounds.

Finally the reaction of the Grignard reagent of o-bromotoluene with 4-methoxyphthalic anhydride gave only one product, presumably 2-(2´-methylbenzoyl)-4-methoxybenzoic acid (XXII).

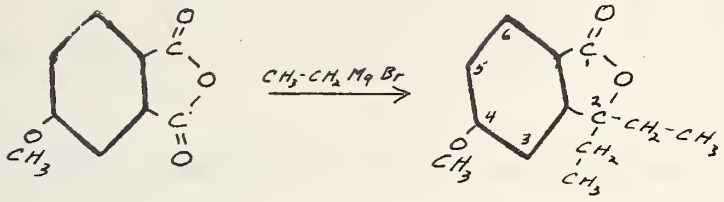


XXII

It was analysed but due to lack of material could not be fully characterized at the present time.

It becomes evident that only one product rather than the expected two products, is obtained in the reaction of a Grignard reagent with 4-methoxyphthalic anhydride. The results here are in agreement with the work of Bauer (10). In the reaction of ethylmagnesium bromide

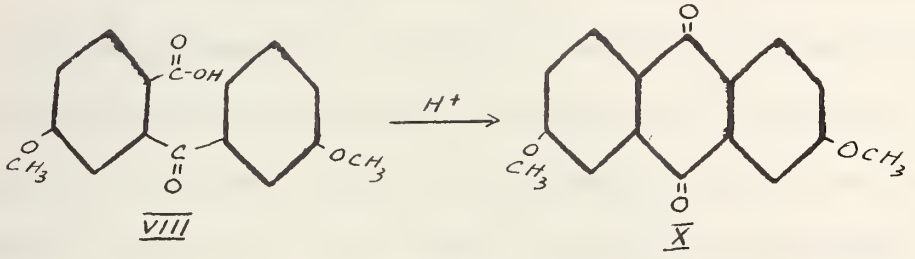
with this anhydride he found that only the carbonyl meta to the methoxy group was attacked with subsequent formation of 4-methoxydiethylphthalide (XXIII).



XXIII

The work of Weizmann et al (9) and Bauer (10) are the only examples cited in the literature of the use of a 4 substituted phthalic anhydride in the Grignard reaction and indeed both involve the 4-methoxy compound.

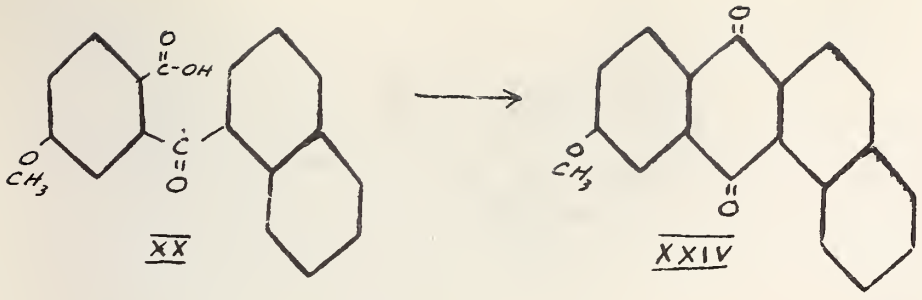
As to the preparation of the dimethoxyanthraquinone it was found that cyclization of VIII with either hot concentrated sulfuric acid or phosphorus pentoxide in nitrobenzene, gave the apparently anomalous result of producing, in good yield, one quinone rather than the expected four. That product was the 2,7-dimethoxy compound (X).



VIII X

The latter was characterized by carrying out a mixed melting point with an authentic sample. Further, X was reduced to the dimethoxyanthracene whose melting point agreed with that reported in the literature.

Cyclization of 2-naphthoyl-4-methoxybenzoic acid XX afforded only 7-methoxy-1,2-benzanthraquinone (XXIV).



XX XXIV

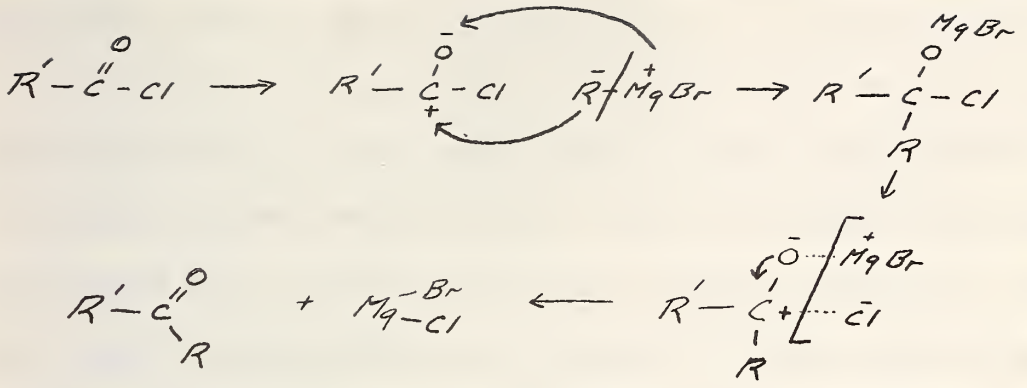
The yield of this quinone was poor but, nevertheless, it was the only pure product isolated from the cyclization reaction mixture.

That only one product resulted in both of the above cyclizations indicates that no rearrangement of either VIII or XX occurs as did occur with examples previously cited.

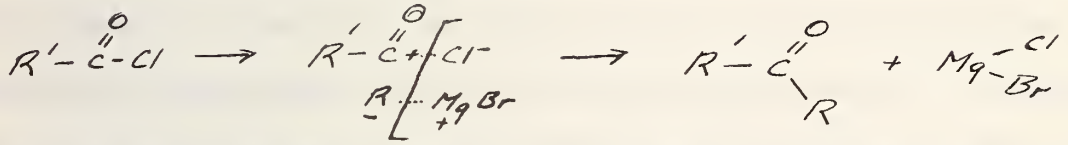
DISCUSSION

Consideration of the experimental results show that in the reaction of a Grignard reagent with 4-methoxyphthalic anhydride, certain forces are acting within the molecule of the latter which prevent the formation of the two expected products.

The explanation given here for this result must be preceded by certain considerations of Grignard reactions with acid anhydrides and acyl halides which, in fact, are mixed acid anhydrides. In the reaction of a Grignard reagent with an acyl halide it has been suggested that the reaction may occur through two different mechanisms. The first mechanism is by the preliminary addition of the organometallic to the carbonyl of the acyl halide followed by splitting out of magnesium halide. If the reaction were thought to be ionic in nature it would presumably follow the path indicated in the following equation.

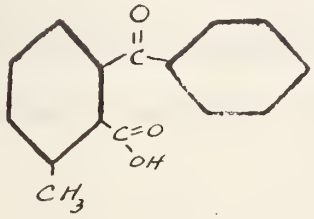


The alternate mechanism is through the direct replacement of the halogen.

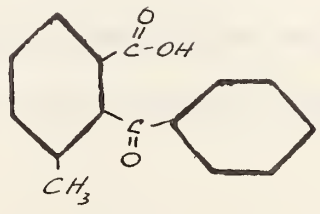


Gilman (11) suggests that the favored mechanism is the addition mechanism and not the metathetical, in view of the fact that acyl fluorides react more readily than do chlorides which in turn are more reactive than the bromides. If the reaction were metathetical this order should be reversed since "other halides show rather consistently that the order of decreasing reactivity of halogens in carbon halogen linkages is: C-Br, C-Cl, C-F."

As pointed out earlier Newman and McLeary (3a) have carried out the reaction between 3-methylphthalic anhydride and phenylmagnesium bromide. This afforded a 44% yield of IV and a 14% yield of V.

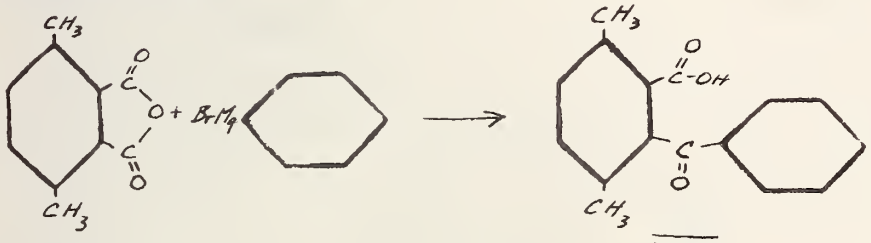


IV



V

Newman and Lord (3b) suggest that if this occurred merely through preliminary addition of the Grignard reagent to a carbonyl double bond of the anhydride, then the yield of V should be much lower than that found experimentally, since such a reaction would require addition to the highly hindered carbonyl which is ortho to the methyl substituent. They suggest that such could occur only with great difficulty. Further they suggest that the metathetical reaction (i.e. the split of the C-O single bond) competes successfully with the addition mechanism. Obviously such a metathetical reaction would not be so subject to hindrance by the methyl group. To bear this out they point out that if the addition mechanism predominated or were the sole mechanism then such a reaction with 3,6-dimethylphthalic anhydride (XXV) should give a negligible yield of keto acid XXVI.

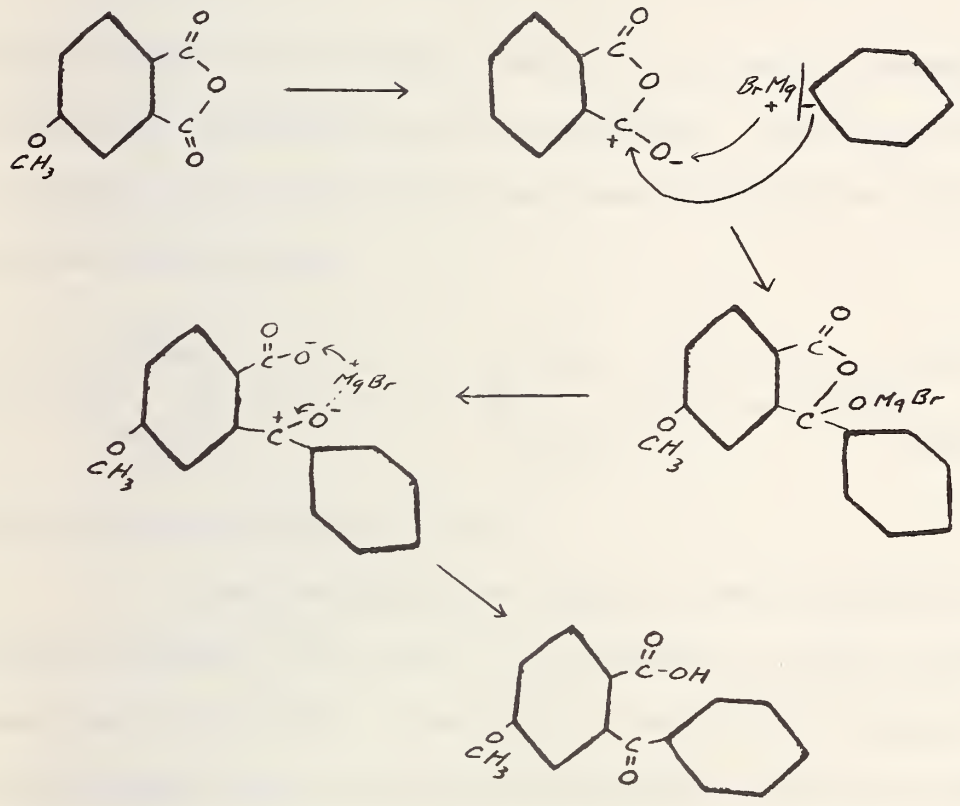


XXV XXVI

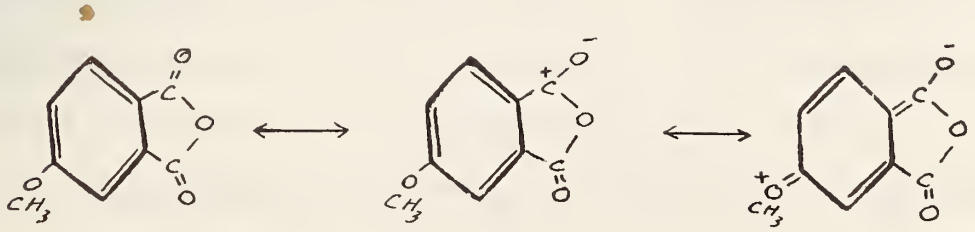
Experimentally XXVI is obtained in 80% yield.

The present work does not refute this reasoning, but in view of the experimental results obtained with 4-methoxyphthalic anhydride, it is suggested here, that when no hindering groups are carried by the phthalic anhydride reagent or if such hindering effect be diminished by having the substituent at the 4 position of the anhydride then the addition mechanism indeed not only predominates but may be the sole mechanism in effect. For example in the reaction of phenylmagnesium

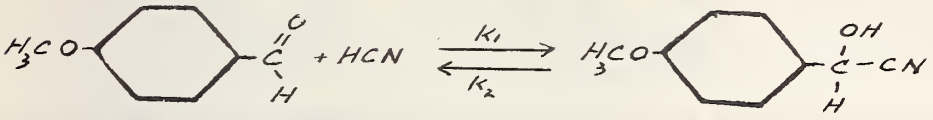
bromide with 4-methoxyphthalic anhydride where little or no hindrance is effected by the methoxy group, the benzoyl group is established at the 2 position. This would stipulate that addition of the Grignard reagent take place at the carbonyl in position 2 which is meta to the methoxy group. This mechanism may be represented as follows:



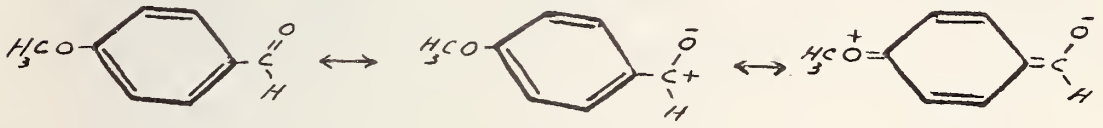
That such addition does not take place at the carbonyl in position 1 may be accounted for by considering the high degree of resonance stabilization of that carbonyl effected by the methoxy group para to it. Resonance among the three structures below would preclude the possibility of addition to that carbonyl.



The suggestion of such resonance stabilization in this anhydride molecule is consistent with certain data found by Manske regarding cyanohydrin formation with para substituted benzaldehydes. In the reaction



k_2 was found to be very large compared to k_2 for the corresponding system with benzaldehyde and its cyanohydrin. Branch and Calvin (12)(a) interpret this as being due to resonance stabilization of the carbonyl by the methoxy group.



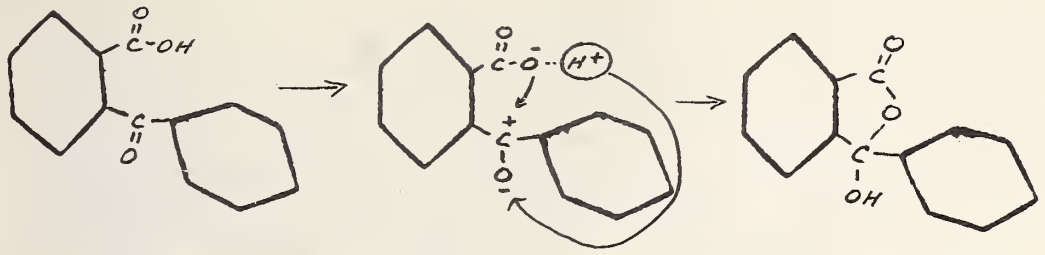
This hinders addition of the HCN.

Such reasoning also applies to the alcoholysis of p-methoxybenzoyl chloride. The rate of this reaction is greatly decreased as compared to the similar alcoholysis of unsubstituted benzoyl chloride. A SUBSTITUENT WHICH IS CAPABLE OF STABILIZING A POSITIVE CHARGE, REDUCES THE RATE OF REACTION THROUGH LOWERING THE FREE ENERGY OF THE REACTANT (12)(b).

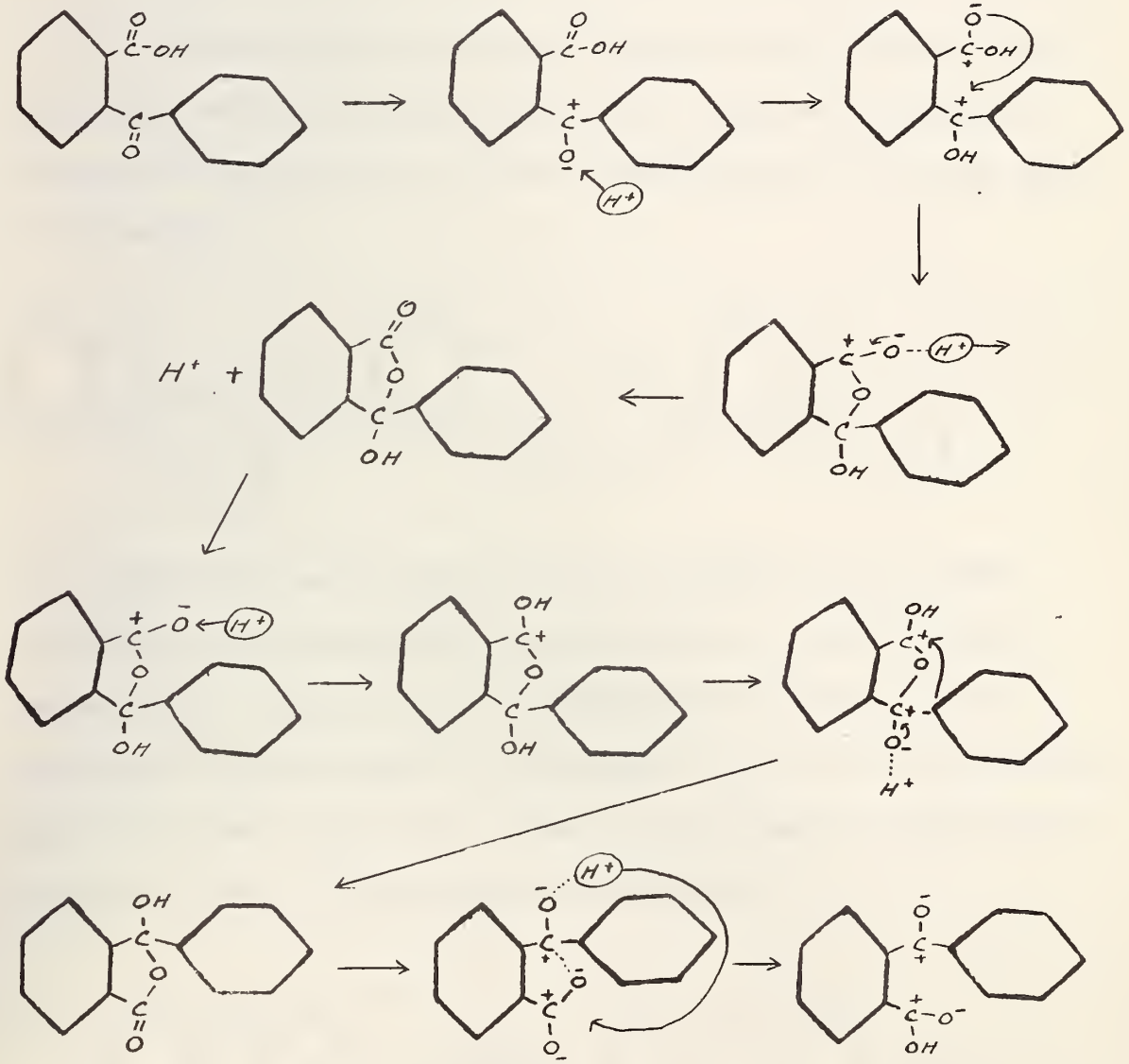
The present experimental results show that independent of the nature of the Grignard reagent reacted with the 4-methoxyphthalic anhydride, the aroyl group is established at the 2 position.

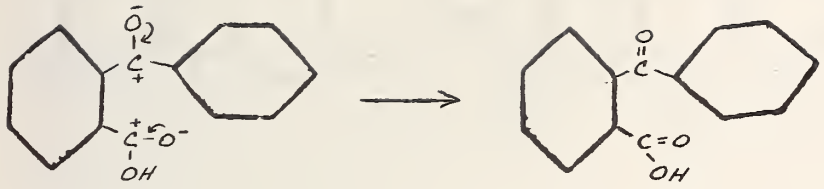
The fact that in the cyclization of 2-(3′-methoxybenzoyl)-4-methoxyphthalic acid only one product, 2,7-dimethoxyanthraquinone, is afforded, indicates that no rearrangement of that keto acid occurs through the $\alpha - 6$ migration of the methoxyphenyl group. It will be recalled that Cook's explanation for a rearrangement of this sort, presupposes a

formation of the intermediate hydroxylactone structure:

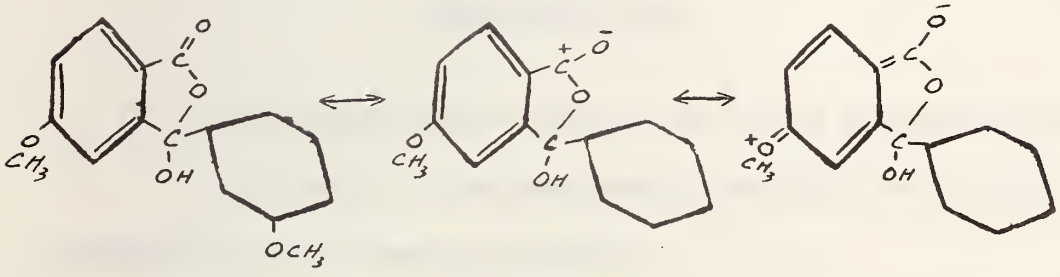


The actual rearrangement is evidently acid catalysed and the following mechanism is suggested here. It necessitates first the addition of a proton to a carbonyl.

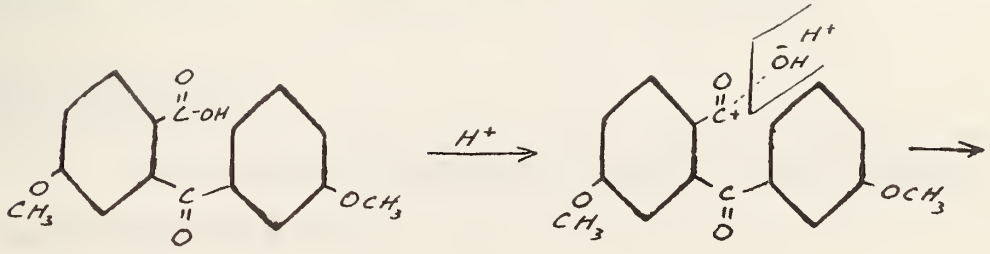


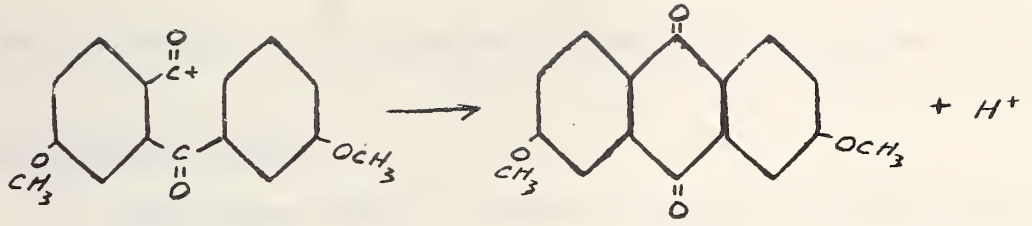


The fact that no such rearrangement occurs when the benzoic acid nucleus carries a methoxy group in the 4 position may again be accounted for on the basis of resonance stabilization of carbonyl para to that methoxy.



This stabilization would greatly hinder the addition of the proton postulated to be necessary for the rearrangement. This would allow the keto acid to cyclize in a straightforward manner in preference to permitting the rearrangement to the isomeric keto acid. The cyclization could then proceed through the attack of a carbonium ion (derived from the carboxyl group) upon the adjacent benzene ring.



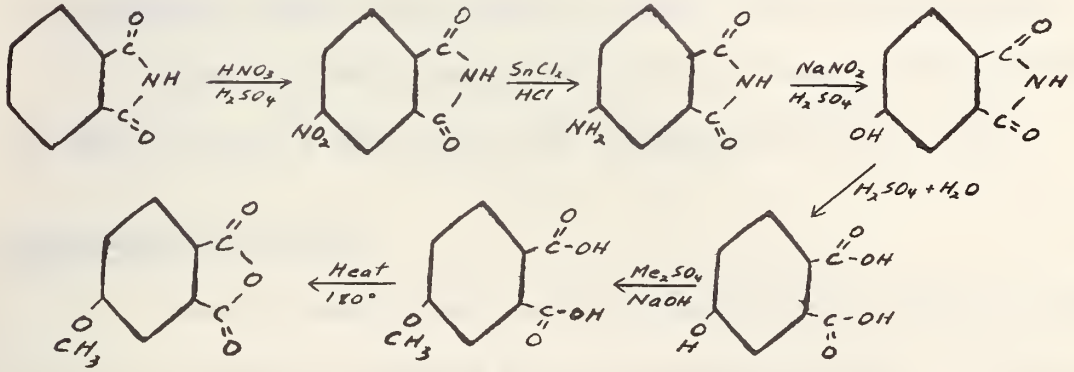


That no cyclization occurs at a position ortho to the methoxy group may be accounted for on the simple basis of steric hindrance. Reaction at a para position is consistently favored over reaction at an ortho position.

EXPERIMENTAL PART

All melting points and boiling points are uncorrected.

The required 4-methoxyphthalic anhydride was prepared according to the following flowsheet.



4-Nitrophthalimide

This compound was prepared according to the procedure given in Organic Syntheses (13).

4-Aminophthalimide

This amine was obtained by reducing the corresponding nitro compound according to the directions of Rodionow and Fedorowa (14).

4-Hydroxyphthalic Acid

Eighty four grams of 4-aminophthalimide was dissolved in 325 cc. of concentrated sulfuric acid and the solution was cooled to 5°. Forty grams of finely powdered sodium nitrite was added very slowly, with mechanical stirring, to this acid solution. When the addition was completed, the resulting mixture was poured, with vigorous shaking, into a kilogram of cracked ice. This solution was allowed to stand at 0°-5° for one-half hour to insure complete diazotization and was then heated on the steam cone until bubbles of nitrogen ceased to come off.

The heating process accomplishes not only the hydrolysis of the diazonium group to a hydroxyl but also the hydrolysis of the imide linkage to the free carboxyl groups.

The warm hydrolysate was treated with norite, filtered, cooled and thoroughly extracted with ether. The combined extracts were dried over anhydrous sodium sulfate and the ether finally distilled off.

This afforded an excellent yield of crude 4-hydroxy phthalic acid which melted at about 190°-195° (reported 204°-205°) (14).

4-Methoxyphthalic Acid

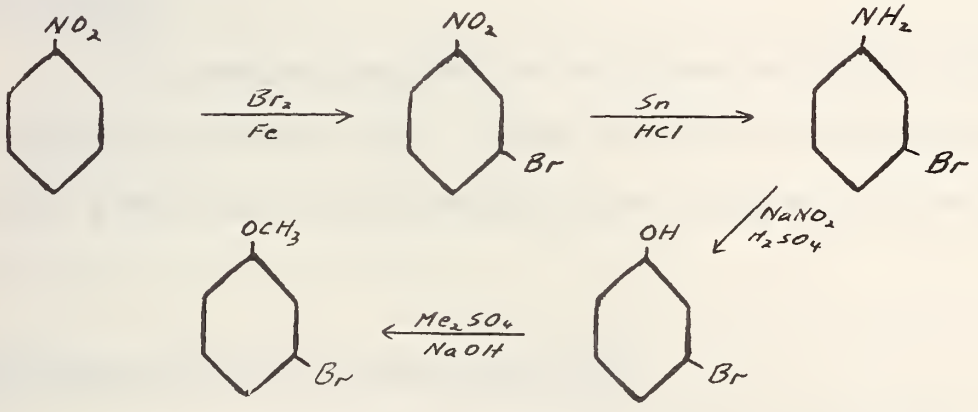
Twenty grams of the crude 4-hydroxyphthalic acid was dissolved in 150 cc. of water containing 20 g. of sodium hydroxide. To this solution 35 g. of methyl sulfate was added dropwise with mechanical stirring. An additional 30 cc. of approximately 30% sodium hydroxide solution was added all at once and this was followed by the dropwise addition of 35 g.

more of methyl sulfate. To complete the reaction the solution was heated on the water bath with mechanical stirring for an additional thirty minutes, cooled, acidified with concentrated hydrochloric acid, allowed to stand at 0° for some hours and the solid material filtered. It was crystallized once from water, using norite, and afforded a 40% to 60% yield of 4-methoxyphthalic acid m.p. 165°-166° (reported 165°). This product retained a slight orange coloration but was pure enough for conversion to the anhydride.

4-Methoxyphthalic Anhydride

An excellent yield of this compound was obtained by heating 4-methoxyphthalic acid at 175°-180° for forty-five minutes. The crude product was crystallized from benzene-ligroin. This pure product melted at 96° (reported 98°).

The required m-bromoanisole was prepared according to the following flow sheet.



m-Bromonitrobenzene

This compound was prepared according to the method given in Organic Syntheses (15).

m-Bromoaniline

m-Bromonitrobenzene was reduced with tin and hydrochloric acid according to the directions of Natelson and Gottfried (16). A good yield of crude m-bromoaniline was obtained.

m-Bromophenol

A solution of 55 g. of crude m-bromoaniline in 35 cc. concentrated sulfuric acid and 150 cc. of water was cooled to 0°-5° and diazotized in the usual manner with a solution of 25 g. sodium nitrite in 90 cc. of water. After having destroyed the excess nitrous acid with urea the solution was filtered, an additional 50 cc. of concentrated sulfuric acid added, and the solution was heated on the steam cone until nitrogen ceased to come off.

Ether extraction of the cooled solution afforded 50 g. of crude m-bromophenol.

m-Bromoanisole

The crude m-bromophenol was methylated according to the directions of Natelson and Gottfried (16). Vacuum distillation of the crude product afforded a 50% yield of pure m-bromoanisole boiling at 103°-108° and 21 mm.

2-(3′-Methoxybenzoyl)-4-methoxybenzoic Acid

The Grignard reagent prepared from 15 g. of m-bromoanisole and 3 g. of magnesium in 50 cc. of anhydrous ether and 50 cc. of anhydrous, thiophene-free benzene was added rapidly to a well stirred solution of 15 g. of 4-methoxyphthalic anhydride in 300 cc. of warm thiophene-free

benzene. The mixture was refluxed for two hours, cooled, treated with dilute hydrochloric acid and the benzene-ether layer was separated and extracted thoroughly with sodium bicarbonate solution. Acidification of the soda extracts afforded the crude keto acid which on crystallization from 50% acetic acid gave 7 g. (30%) of almost pure 2-(3′-methoxybenzoyl)-4-methoxybenzoic acid. For analysis it was crystallized three times from benzene and melted at 173°.

Anal. Calcd. for $C_{16}H_{14}O_5$: C, 67.1; H, 4.9. Found: C, 67.1; H, 4.9.

By way of characterization of this keto acid 8 g. of it was decarboxylated by heating with basic copper carbonate for one hour at a temperature of 260°. The product was distilled at reduced pressure and afforded 6 g. of the 3,3′-dimethoxybenzophenone, a yellow, very viscous liquid boiling at 164°-168° and 2 mm. (reported 230°-235° and 20 mm.) (17).

One gram of this dimethoxy compound was boiled under reflux, for three hours, with 10 cc. of 55% hydriodic acid. The mixture was diluted with 50 cc. of water, decolorized with sodium bisulfite and the solid material filtered. On crystallization from water this solid afforded 0.6 g. of 3,3′-dihydroxybenzophenone, m.p. 160°-161° (reported 162°-163°) (18).

2-Benzoyl-4-methoxybenzoic Acid

The Grignard reagent of phenyl bromide was added to an equimolar quantity of 4-methoxyphthalic anhydride and the reaction mixture worked up in the manner described above. The crude product was crystallized three times from 50% acetic acid and afforded a 30% yield of 2-benzoyl-4-methoxybenzoic acid, m.p. 172°. Weizmann et al (9) give analytical data for this compound and record a yield of 80% and melting

point of 167° but these workers neglected to characterize the product.

In the present work this compound was characterized by decarboxylating in the presence of basic copper carbonate, distilling the resulting 3-methoxybenzophenone and demethylating the latter with 55% HI. The product, 3-hydroxybenzophenone, was crystallized from dilute ethanol and melted at 115° (reported 116°).

2-Naphthoyl-4-methoxybenzoic Acid

This compound was prepared from the Grignard reagent of 1-bromonaphthalene and 4-methoxyphthalic anhydride. Crystallization of the crude product from glacial acetic acid afforded 2-naphthoyl-4-methoxybenzoic acid, m.p. 192°-193° (reported 196°) (9).

Seven grams of this acid was decarboxylated and the product, 1-naphthyl-3-methoxyphenyl ketone, was distilled at reduced pressure. The yield of this brightly yellow colored oil was 5 g. and it boiled at 260°-261° and 24 mm.

The above ketone (1.3 g.) was fused with 1.5 g. of potassium hydroxide according to the directions of Bachmann (8). The cooled mass was taken up in boiling water and filtered. The precipitate gave no depression of the melting point when mixed with an authentic sample of naphthalene. The warm, alkaline filtrate was acidified and the resulting precipitate was immediately filtered. The latter was crystallized twice from dilute acetic acid and afforded only several mg. of what was identified by a mixed melting point as 1-naphthoic acid, m.p. 156°-157°. The filtrate which was obtained, with the separation of the naphthoic acid, was thoroughly cooled and afforded a considerable quantity of

m-methoxybenzoic acid. It melted at 104°-105° and gave no depression of the melting point when mixed with an authentic sample of m-methoxybenzoic acid.

1-Naphthyl-(2-carboxy-5-methoxyphenyl)methane

One gram of 2-naphthoyl-4-methoxybenzoic acid was reduced with zinc dust and potassium hydroxide according to the procedure used by Nichol and Sandin (5). This afforded 0.8 g. of the almost pure methane derivative. For analysis it was crystallized from glacial acetic acid and melted at 174°-175°.

Anal. Calcd. for $C_{19}H_{16}O_3$: C, 78.1; H, 5.5. Found: C, 77.9; H, 5.8.

2-(2′-Methylbenzoyl)-4-methoxybenzoic Acid

The reaction of the Grignard reagent of o-bromotoluene with 4-methoxyphthalic anhydride gave this compound. The crude product was crystallized twice from glacial acetic acid and separated as white needles, m.p. 166°-167°.

Anal. Calcd. for $C_{16}H_{14}O_4$: C, 71.2; H, 5.2. Found: C, 70.9; H, 5.4.

2,7-Dimethoxyanthraquinone

Three grams of 2-(3′-methoxybenzoyl)-4-methoxybenzoic acid was dissolved in 30 cc. of concentrated sulfuric acid and the solution was heated on the steam bath for three hours. The deep purple solution which resulted was poured into cracked ice and the dirty yellow product was filtered. This solid was washed by decantation with sodium bicarbonate solution, then with water, filtered, dried and crystallized twice from acetic acid. The product, 2,7-dimethoxyanthraquinone, was thus obtained, in 60% yield, as beautiful yellow needles, m.p. 212°-213°

(reported 211°). A mixed melting point with an authentic sample was not depressed. The latter sample was prepared from 2,7-diaminoanthraquinone (19) by tetrazotization, hydrolysis of the tetrazonium salt and methylation of the resulting dihydroxy compound with methyl sulfate and sodium hydroxide solution.

To insure that cyclization of the keto acid gave only one product, a sample of the acid was cyclized by heating with phosphorous pentoxide in nitrobenzene according to the directions of Cook (7). Only the 2,7-dimethoxyanthraquinone was produced and in 65% yield. This cyclization proved superior both from the standpoint of yield and purity of product.

2,7-Dimethoxyanthracene

One gram of the above quinone was reduced with zinc dust, sodium hydroxide solution and toluene according to the general procedure developed by Martin (20) for the reduction of anthraquinones. The hydrocarbon was obtained in 65% yield and melted at 212°-213° (reported 216°-217°).

7-Methoxy-1,2-benzanthraquinone

Cyclization of 2 g. of 2-naphthoyl-4-methoxybenzoic acid with phosphorous pentoxide in nitrobenzene afforded 1.6 g. of a crude yellow solid. This was crystallized once from dilute acetic acid and four times from 95% ethanol. The brightly yellow colored quinone was thus obtained in approximately 20% yield and melted at 172°-173°.

Anal. Calcd. for $C_{19}H_{12}O_3$: C, 79.1; H, 4.2. Found: C, 78.6; H, 4.4.

No other pure compound could be isolated from the crystallization liquors.

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